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## **Differentiated thyroid carcinoma. Follow-up of 264 patients from one institution for up to 25 years**

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**Abstract:** UNLABELLED The optimum treatment for differentiated thyroid carcinoma (DTC) is still debated. Results obtained using a selective treatment strategy for papillary (PTC) and follicular (FTC) thyroid carcinoma over 25 years in one institution are reported. 149 patients (mean age 46 yrs) had PTC in TNM stages I-IV in 58%, 26%, 15% and 1% respectively. Total thyroidectomy and remnant 131I ablation (43%) were carried out in TNM high-risk patients (stages III and IV) and in low-risk patients (I and II) at risk for a (curable) recurrence (stages pN1 and/or pT4). Hemi- or total thyroidectomy, without radioiodine, was used in 76% of pT1-3 N0 tumours (68%). Central and/or lateral lymphadenectomy was performed in 42% of patients (electively in the last 4 years). The mean follow-up was 7 years. **RESULTS** 6 patients died of PTC and 8/143 patients treated for cure had a recurrence (6 nodal, 1 contralateral, 1 local). In low-risk patients—including 68% of patients aged  $\geq 45$  yrs—the cause specific 25-year survival rate was 100%, vs. 62% (at 15 years) ( $p < 0.0001$ ) in high-risk patients. In stage I and stage II the recurrence-free survival rates at 25 years were 95% and 100% respectively. Risk factors for recurrence were macroscopic ( $p < 0.0001$ ) but not microscopic local invasion (pT4); stage pN1 ( $p = 0.0004$ ). Only 1/107 patients initially judged node-negative had a nodal recurrence. FTC ( $n = 115$ ; mean age 56 yrs; mean follow-up 8 yrs): Cause-related death ( $n = 8$ ) or serious recurrence ( $n = 3$ ) occurred in 10/53 grossly invasive FTC, in 1/45 minimally invasive FTC with vascular invasion, and in none of 17 FTC with capsular invasion (CI) alone, under radical treatment (131I) in 75%, 33%, and 12% respectively. 20-year disease-free survival in grossly and in minimally invasive FTC was 78% and 95.5% respectively ( $p = 0.0007$ ). Patients aged  $< 45$  yrs and patients with minimally invasive FTC with CI alone (all ages) had 100% 20-year disease-free survival vs. 80% ( $p = 0.013$ ) in the remainder. There was no curable recurrence in FTC. The ratio of grossly invasive FTC decreased ( $p < 0.0001$ ) during the study period. **CONCLUSIONS** Risk-0 groups may be defined and selected for a reduced extent of treatment (PTC pT1-3 N0; FTC  $< 45$  yrs, or CI alone). Older ( $\geq 45$  yrs) patients with PTC in stages I and II have an excellent prognosis (risk 0). With selective (therapeutic) lymphadenectomy the risk of nodal recurrence may be very low in node negative tumours, without use of radioiodine. Meticulous lymphadenectomy is indicated in pN1 tumours with nodal recurrences despite 131I (5/36 patients). The technique of capsular dissection for extracapsular total uni- or bilateral thyroidectomy provides excellent oncological and surgical results. A decrease in the incidence of FTC parallels a decrease in endemic goitre in Switzerland.

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# Differentiated thyroid carcinoma

## Follow-up of 264 patients from one institution for up to 25 years

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## Summary

The optimum treatment for differentiated thyroid carcinoma (DTC) is still debated. Results obtained using a selective treatment strategy for papillary (PTC) and follicular (FTC) thyroid carcinoma over 25 years in one institution are reported. 149 patients (mean age 46 yrs) had PTC in TNM stages I–IV in 58%, 26%, 15% and 1% respectively. Total thyroidectomy and remnant <sup>131</sup>I ablation (43%) were carried out in TNM high-risk patients (stages III and IV) and in low-risk patients (I and II) at risk for a (curable) recurrence (stages pN<sub>1</sub> and/or pT<sub>4</sub>). Hemi- or total thyroidectomy, without radioiodine, was used in 76% of pT<sub>1-3</sub> N<sub>0</sub> tumours (68%). Central and/or lateral lymphadenectomy was performed in 42% of patients (electively in the last 4 years). The mean follow-up was 7 years. **Results:** 6 patients died of PTC and 8/143 patients treated for cure had a recurrence (6 nodal, 1 contralateral, 1 local). In low-risk patients – including 68% of patients aged ≥45 yrs – the cause specific 25-year survival rate was 100%, vs. 62% (at 15 years) ( $p < 0.0001$ ) in high-risk patients. In stage I and stage II the recurrence-free survival rates at 25 years were 95% and 100% respectively. Risk factors for recurrence were macroscopic ( $p < 0.0001$ ) but not microscopic local invasion (pT<sub>4</sub>); stage pN<sub>1</sub> ( $p = 0.0004$ ). Only 1/107 patients initially judged node-negative had a nodal recurrence. FTC ( $n = 115$ ; mean age 56 yrs; mean follow-up 8 yrs): Cause-related death ( $n = 8$ ) or serious recurrence ( $n = 3$ ) occurred in 10/53 grossly invasive FTC, in 1/45 minimally invasive FTC with vascular invasion, and in none of 17 FTC with

capsular invasion (CI) alone, under radical treatment (<sup>131</sup>I) in 75%, 33%, and 12% respectively. 20-year disease-free survival in grossly and in minimally invasive FTC was 78% and 95.5% respectively ( $p = 0.0007$ ). Patients aged <45 yrs and patients with minimally invasive FTC with CI alone (all ages) had 100% 20-year disease-free survival vs. 80% ( $p = 0.013$ ) in the remainder. There was no curable recurrence in FTC. The ratio of grossly invasive FTC decreased ( $p < 0.0001$ ) during the study period.

### Conclusions:

- Risk-0 groups may be defined and selected for a reduced extent of treatment (PTC pT<sub>1-3</sub> N<sub>0</sub>; FTC <45 yrs, or CI alone).
- Older (≥45 yrs) patients with PTC in stages I and II have an excellent prognosis (risk 0).
- With selective (therapeutic) lymphadenectomy the risk of nodal recurrence may be very low in node negative tumours, without use of radioiodine. Meticulous lymphadenectomy is indicated in pN<sub>1</sub> tumours with nodal recurrences despite <sup>131</sup>I (5/36 patients).
- The technique of capsular dissection for extra-capsular total uni- or bilateral thyroidectomy provides excellent oncological and surgical results.
- A decrease in the incidence of FTC parallels a decrease in endemic goitre in Switzerland.

**Keywords:** papillary thyroid cancer; follicular thyroid cancer; selective therapy; prognostic TNM classification; capsular dissection; 25-year follow-up

## Introduction

Differentiated thyroid carcinomas (DTC) are biologically unique tumours. Prognostic classifications serve to segregate a majority of patients with near-0 risk of tumour-related death from a minority at much greater risk [1–8]. Major risk factors are patient's age, tumour size, grade, extent (inva-

sion) (pT<sub>4</sub>), metastases (M<sub>1</sub>), and completeness of resection for papillary (PTC), and invasiveness for follicular (FTC) thyroid carcinoma [9–14]. Several prognostic classification systems based upon these factors (AGES, AMES, MACIS, age-related TNM classification) [1, 2, 5, 13, 15] have proven

useful for defining low-risk and high-risk patients; less appropriate systems do not consider age [16, 17], albeit the most important prognostic factor. On the basis of prognostic classification, treatment results may be compared and patients selected for a risk-related scale of treatment. Selective treatment is now widely considered appropriate [1, 2, 6, 7, 12, 14, 18, 19–23]. In low-risk patients with PTC adequate treatment should also prevent (cur-

able) recurrences, which are most frequent in tumours with nodal (pN<sub>1</sub>) or locally invasive (pT<sub>4</sub>) disease at diagnosis [5, 21].

This study of 149 patients with PTC and 115 patients with FTC from one institution over a period of 25 years confirms that low-risk patients can be defined in whom no tumour-related deaths and very few curable recurrences are observed after selective risk-dependent therapy.

## Patients and methods

A total of 264 unselected consecutive patients with DTC were treated and followed up from 1974 to 1999. The records of 166 patients described previously [19] have been updated. Clinical and diagnostic aspects have been reported recently [20]. The patients were operated on by one surgeon (E.G.) or with his assistance. The histopathological assessment was conducted prospectively by one pathologist (Ph.U.H.) and his staff according to the WHO classification [13, 19]. PTC were classified according to the age-related prognostic TNM-classification system [24] (Table 1). Extrathyroidal (pT<sub>4</sub>) PTC were subdivided into gross invasion based on macroscopic intraoperative evidence (pT<sub>4</sub> ma), and thyroid capsular penetration as a microscopic finding only (pT<sub>4</sub> mi). Follicular carcinomas (FTC) were classified as minimally or grossly invasive [3, 4, 13]; minimally invasive FTC were subdivided into those with vascular invasion (VI), and those with exclusively capsular invasion (CI) [10, 13].

The treatment strategy consisted in a restricted interventional approach in selected low-risk patients [19, 20]<sup>1</sup>. 120/264 (45%) patients underwent total thyroidectomy with radioiodine. Total thyroidectomy (n = 184) was achieved in 62 patients (34%) by completion thyroidec-

tomy, after definitive histological diagnosis. Some patients (7%) refused completion total thyroidectomy or use of radioactive iodine, as proposed by the therapeutic scheme. Up to 1995 lymphadenectomy was performed for macroscopically involved nodes (selective therapeutic lymphadenectomy). From 1996 an elective routine (diagnostic, prophylactic) lymphadenectomy of the central compartment was introduced for pre- or intraoperatively confirmed PTC [25]. Technically complete extracapsular (no subtotal or near total) lobar excision was performed by capsular dissection [20, 26, 27] on the side of a suspicious or carcinomatous nodule.

261/264 patients were followed up 0.5–25 years. Mean follow-up was 7 years (median 6) for PTC, and 8 years (median 7) for FTC. 14 patients had died from thyroid carcinoma and 28 from unrelated causes without tumour manifestation. 10 patients had been lost since the last follow-up.

## Data analysis

For statistical analyses the programs Stat View 4.51 (Abacus Concepts, Inc.) and SPSS for Macintosh Release 6.1.1 were used. Continuous variables are presented as mean ± standard deviation and were analysed using the Mann-Whitney test. Nominal variables are presented as number of patients (%) and were compared using the chi-square test or Fisher's exact test when appropriate.

Late results were analysed using the method of Kaplan and Meier.

Survival curves were compared using the log-rank test. The effect of tumour diameter on survival curves was analysed using Cox regression. P-values below 0.05 are considered significant.

**Table 1**

Age-related TNM classification system. From UICC [24]. pT<sub>1</sub>: <1 cm; pT<sub>2</sub>: >1–4 cm; pT<sub>3</sub>: >4 cm; pT<sub>4</sub>: extends beyond gland; N<sub>1</sub>: regional lymph node metastasis; M<sub>1</sub>: distant metastasis.

Stage	age <45 years	age ≥45 years
I	pT <sub>1-4</sub> N <sub>0,1</sub> M <sub>0</sub>	pT <sub>1</sub> N <sub>0</sub> M <sub>0</sub>
II	pT <sub>1-4</sub> N <sub>0,1</sub> M <sub>1</sub>	pT <sub>2-3</sub> N <sub>0</sub> M <sub>0</sub>
III		pT <sub>4</sub> N <sub>0</sub> M <sub>0</sub>
		pT <sub>1-4</sub> N <sub>1</sub> M <sub>0</sub>
IV		pT <sub>1-4</sub> N <sub>0,1</sub> M <sub>1</sub>

## Results

During the study the ratio of PTC increased from 35% to 66% (p = 0.03), whereas that of grossly invasive FTC decreased from 41% to 9% (p < 0.0001) [20]. A concomitant benign nodular goitre was more frequent in patients with a grossly invasive FTC than in PTC (45% vs. 18%; p = 0.002); the same was true for nodular goitre with functional autonomy (19% vs. 3%; p = 0.0007) [20].

<sup>1</sup> hemi- or total thyroidectomy for (a) PTC pT<sub>1,2,3</sub> N<sub>0</sub>, (b) minimally invasive FTC pT<sub>1,2</sub> age <45 yrs, or CI alone; total thyroidectomy and <sup>131</sup>I remnant ablation for (a) pT<sub>4</sub> and pN<sub>1</sub> PTC, (b) grossly invasive FTC and minimally invasive FTC age ≥45 yrs

## Papillary carcinoma

### Age groups

68/149 patients (46%) were in the young (<45 yrs) and 81 (54%) in the older age group (≥45 yrs). N<sub>1</sub>-status (27%) was more common in young than in older patients (35% vs. 20%; p = 0.033), and in pT<sub>4</sub> than in pT<sub>1-3</sub> tumours (65% vs. 17%; p < 0.0001). A pT<sub>4</sub> tumour (21%) was found in 18% of young and 23% of older patients (p = ns); gross extrathyroidal invasion was present in 9%.

### M<sub>1</sub> status

All patients with haematogenous metastases (7/149; 5%) had extensive nodal disease (pN<sub>1</sub>), 5

patients had a pT<sub>4</sub> tumour. 5/68 (7%) young patients had diffuse pulmonary radioiodine uptake on the post-remnant ablation scan, and in 2/81 older patients (2.5%) pulmonary metastases were seen on preoperative chest radiography.

### TNM risk groups

86 (58%), 38 (26%), 23 (15%) and 2 (1%) patients were in the TNM risk groups I, II, III and IV respectively, resulting in a low- (I + II) and a high- (III + IV) risk population of 84% vs. 16%. In low- and high-risk patients respectively, extrathyroidal invasion (pT<sub>4</sub>), nodal involvement, and distant disease at primary therapy were present in 12 (10%) vs. 19 (76%), ( $p < 0.0001$ ); 24 (19%) vs. 16 (64%), ( $p < 0.0001$ ), and 5 (4%) vs. 2 (8%), ( $p = \text{ns}$ ).

### Follicular carcinoma

53 patients (46%) had a high-risk (grossly invasive) and 62 patients (54%) a low-risk (minimally invasive) FTC. The ratio has changed to 25% high-risk and 75% low-risk patients ( $p = 0.0003$ ) since 1995, due to the declining rate of grossly invasive FTC. 17 (27%) of minimally invasive FTC had capsular invasion alone. On the average, grossly invasive FTC were 1.6 cm larger in diameter than minimally invasive FTC ( $p < 0.0001$ ), and the patients were 15 years older ( $p < 0.0001$ ). 4 patients (3.5%) had nodal disease and 1 (0.9%) had pulmonary metastases on the initial chest x-ray.

### Node staging, lymphadenectomy

In 62/149 of patients with PTC (42%), and in 15/115 with FTC (13%), central and/or lateral lymphadenectomy was performed, with pN<sub>1</sub> status in 27% of PTC and 3,5% of FTC. Absence of node metastases was based on macroscopic appearance (cN<sub>0</sub>), without lymphadenectomy, in 58% and 87% respectively. Elective vs. selective lymphadenectomy (PTC) resulted in a significant increase of pN<sub>0</sub> status ( $p = 0.03$ ) and a non-significant increase of N<sub>1</sub> status [20, 25].

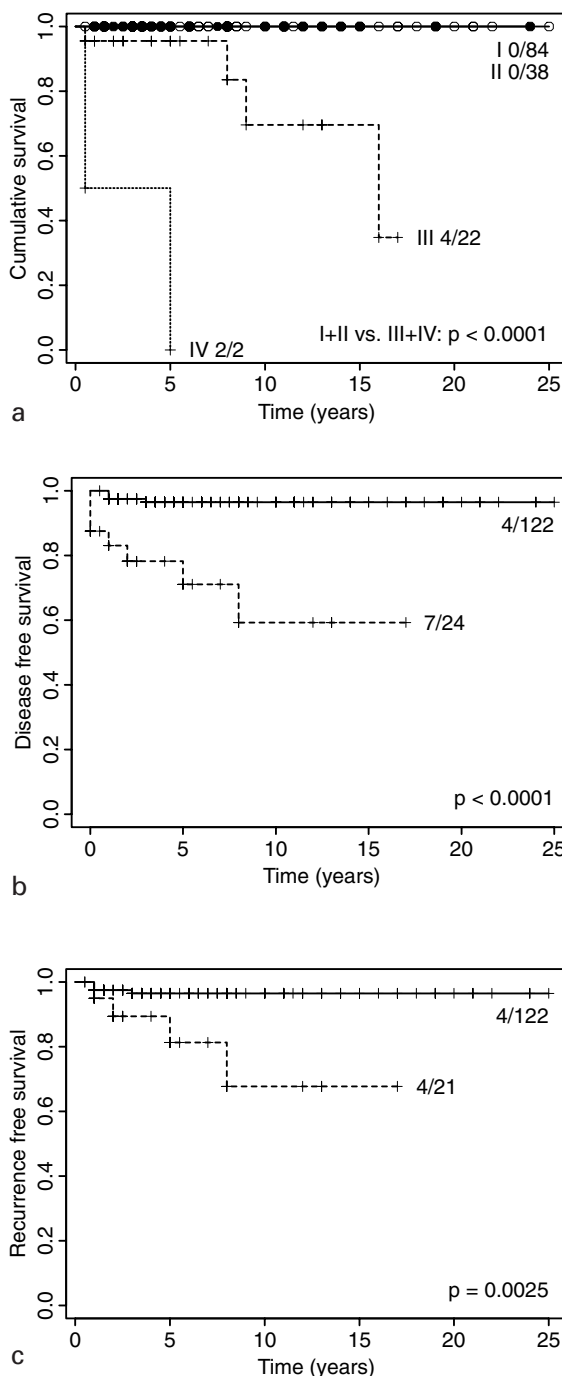
### Treatment results by risk groups

#### Papillary carcinoma ( $n = 146$ , follow-up $\geq 0.5$ yr)

20/24 (83%) of TNM high-risk and 43/122 (35%) of TNM low-risk patients had total thyroidectomy and radioiodine ( $p < 0.0001$ ) (Table 2). All 6 patients who died from carcinoma were in the TNM high-risk category, including 3 patients with non-curative primary treatment. In 8/143 patients a recurrence (1 contralateral, 1 local, and 6 nodal) developed 1–8 years following primary treatment for cure, resulting in death in 3 of the 4 TNM

**Figure 1**

Late results of treatment of PTC.  
a. Cause-specific survival in stages I–IV (I: solid line, open circles; II: solid line, closed circles; III: broken line, +; IV: dotted line, +).  
b. Disease-free survival in TNM low-risk (solid line) and high-risk (broken line) groups.  
c. Recurrence-free survival of patients treated for cure in TNM low-risk (solid line) and high-risk (broken line) groups.



**Table 2**

Papillary thyroid carcinoma ( $n = 146$ ). Primary treatment and outcome, by risk groups. (No of patients [%])

Treatment	TNM stage				total	TNM	
	I	II	III	IV		low risk	high risk
Hemithyroidectomy	26 <sup>a</sup>	8	3 <sup>c</sup>	0	37 (25%)	34	3
Total thyroidectomy	32 <sup>b</sup>	13	1	0	46 (32%)	45	1
Total thyroidectomy, <sup>131</sup> I	26 <sup>b</sup>	17	18 <sup>b,c</sup>	2 <sup>c</sup>	63 (43%)	43 (35%)	20 (83%)
Total	84	38	22	2	146	122 (84%)	24 (16%)

Postoperative events:

curable recurrences ( $n = 5$ ), (occurring 1–3 years after primary therapy):

<sup>a</sup> contralateral ( $n = 1$ ) (pT<sub>2a</sub>N<sub>0</sub>)

<sup>b</sup> nodal ( $n = 4$ ) (1pT<sub>2</sub>N<sub>0</sub>, 2pT<sub>4</sub>N<sub>1</sub> [stage I]; 1pT<sub>1</sub>N<sub>1</sub> [stage III])

deaths ( $n = 6$ ) (occurring 1/2–16 years after primary therapy):

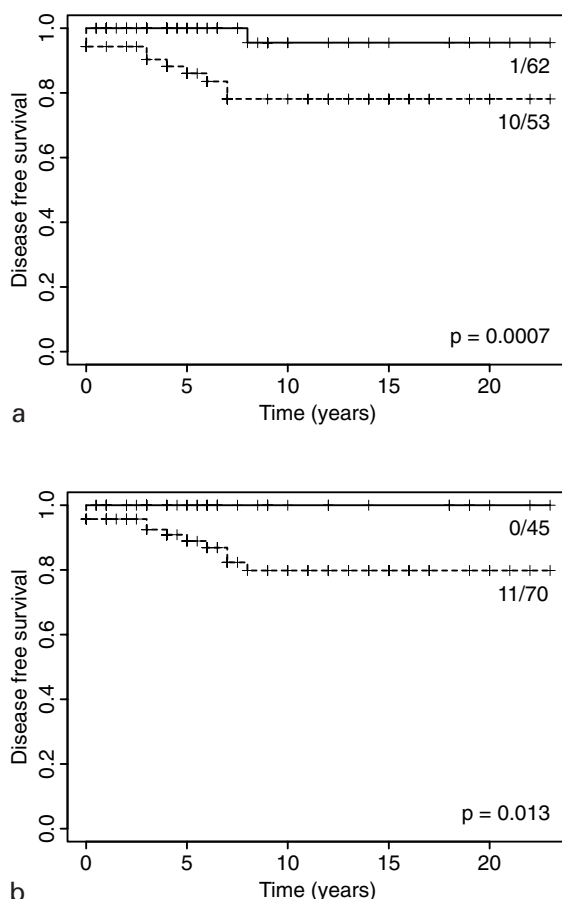
<sup>c</sup> (1pT<sub>4</sub>N<sub>0</sub>, 3pT<sub>3,4</sub>N<sub>1</sub>, 2pT<sub>4</sub>N<sub>1</sub>M<sub>1</sub>)

**Figure 2**

Late results of treatment of FTC.

a. Disease-free survival of patients with minimally invasive (solid line) and with grossly invasive (broken line) FTC.

b. Disease-free survival of patients with CI alone or age <45 years (solid line) compared to remaining patients (broken line) with FTC.



high-risk and in none of the 4 TNM low-risk patients. Thus, there were 5 curable recurrences (Table 2). Only 1/107 nodal recurrence was observed in patients with a primary node negative tumour, vs. 5/36 with a pN<sub>1</sub> tumour ( $p = 0.0004$ , log-rank test). In 3/83 patients without radical initial therapy a postoperative event occurred (1 death; 2 curable recurrences, 1 contralateral, 1 nodal).

**Table 3**

Risk factors in PTC ( $n = 146$ ) by univariate analysis.

Variable	survival	disease-free survival	recurrence-free survival
TNM high risk vs. low risk	<0.0001	<0.0001	0.0025
Age $\geq 45$ vs. <45	0.01	ns	ns
Stage T <sub>4</sub> vs. T <sub>1-3</sub>	<0.0001	<0.0001	0.008
Stage T <sub>4</sub> macroscopic vs. T <sub>1-3</sub> , T <sub>4</sub> microscopic	<0.0001	<0.0001	<0.0001
Stage N <sub>1</sub> vs. N <sub>0</sub>	0.001	<0.0001	0.006
Stage M <sub>1</sub> vs. M <sub>0</sub>	0.008	0.009	
Ø cm	0.001	0.005	ns

**Table 4**

Follicular thyroid carcinoma ( $n = 115$ ). Primary treatment and outcome, by risk groups (no of patients [%]).

Treatment	minimally invasive ( $n = 62$ )		grossly invasive ( $n = 53$ )	total
	capsular invasion alone ( $n = 17$ )	vascular invasion ( $n = 45$ )		
Hemithyroidectomy	10	26	5	41
Total thyroidectomy	5	4 <sup>a</sup>	8 <sup>a</sup>	17
Total thyroidectomy, <sup>131</sup> I	2 (12%)		40 <sup>b,c</sup> (75%)	
Total	17	45	53	115

Postoperative events ( $n = 11$ ): deaths ( $n = 8$ ): <sup>a</sup> 1 death; <sup>b</sup> 6 deaths; <sup>c</sup> serious recurrence ( $n = 3$ )

Late results of treatment of PTC are plotted by TNM risk groups in Figure 1. In low-risk patients the cause-specific 25-year survival rate and the disease-free survival rate was 100% and 96.5% respectively, vs. 62% and 59% (at 15 years) respectively in high-risk patients ( $p < 0.0001$ ). Age  $\geq 45$  yrs vs. <45 yrs significantly influenced survival ( $p = 0.01$ ), but not disease-free and recurrence-free survival (Table 3). Macroscopic (pT<sub>4</sub> ma), but not microscopic extrathyroidal invasion was a significant risk factor for outcome in the entire series ( $p < 0.0001$ ), and for recurrence in the low risk (TNM I and II) group ( $p = 0.0002$ ). Stage pN<sub>1</sub> vs. N<sub>0</sub> had a significant impact on outcome. Gender, hemithyroidectomy vs. total thyroidectomy, or use vs. non-use of <sup>131</sup>I did not influence the results.

### Follicular carcinoma

The risk-dependent treatment and the late results are shown in Table 4. In minimally invasive FTC 1/62 patient died, from pulmonary metastases from 12 years after total thyroidectomy. 3/53 patients with grossly invasive FTC died 2-7 years after non-curative primary treatment, and 7 further patients developed a serious recurrence leading to death in 4 patients 6-12 years after primary treatment; the remaining 3 patients are living with disease 4-8 years after radical treatment. Patients with an adverse outcome (11/115) were aged 55-80 (mean 71) years.

The disease-free survival for minimally and for grossly invasive FTC are plotted in Figure 2a. Patients aged <45 yrs or those with CI alone had cumulative survival and disease-free survival of 100% (Fig. 2b, Table 5). In univariate risk factor analyses grossly invasive tumour, stage pT<sub>4</sub>, nodal involvement, and tumour size had an adverse effect on survival and/or disease-free survival (Table 6). The adverse effect of <sup>131</sup>I clearly reflects patient selection.

### Surgical morbidity

One patient, an 83-year-old man (0.4%) died of cardiac failure after operation for a large infiltrating papillary carcinoma. 5/264 patients (1.9%) developed permanent hypoparathyroidism, representing 3% of those with total thyroidectomy. Unilateral recurrent-nerve paralysis developed in 4 patients (1.5%) or in 1% of nerves at risk ( $n = 407$ ). Seven of the 8 patients with morbidity had a concomitant recurrent benign goitre, completion total thyroidectomy, extensive central nodal involvement, or a grossly invasive FTC respectively.



**Table 5**

Cause-specific survival rates in subgroups of FTC.  
( ) = patients at risk.

Survival	minimally invasive	grossly invasive	CI alone or patients <45 yrs
5 yr	100% (35)	96% (42)	100% (27)
10 yr	100% (15)	85% (29)	100% (11)
20 yr	92% (4)	81% (3)	100% (3)

**Table 6**

Risk factors in FTC by univariate analysis.

Variable	survival	disease-free survival
Grossly vs. minimally invasive tumour	ns	0.0007
T <sub>4</sub> vs. T <sub>1-3</sub>	<0.0001	<0.0001
N <sub>1</sub> vs. N <sub>0</sub>	<0.0001	<0.0001
Ø cm	ns	0.05
Use of <sup>131</sup> I vs. no <sup>131</sup> I	ns	0.03
Hemithyroidectomy vs. total thyroidectomy	ns	ns

## Discussion

This study has the advantages of precise prospective documentation and uniform conditions with respect to surgery and pathology. The duration of follow-up was relatively short, due to an increasing number of annually referred patients. However, though late deaths may occur [9], curable recurrences and those heralding an unfavourable course are seen most frequently during the first 5–10 years [5, 9, 21, 22] – 1–8 years in our 16/255 patients with primary therapy for cure.

During the 25-year period the proportion of FTC decreased significantly, from 65% to 34% of all DTC, due to a decrease in grossly invasive FTC. Therefore, PTC became the most frequent tumour. For the 30-year period 1944–1973 a decrease in FTC from 52% to 38% was found in a series of 550 pathological specimens of thyroid carcinoma in Switzerland [28]. These data reflect a continuous decrease in the incidence of FTC, which parallels a decrease in the prevalence of simple goitre [29] and of its toxic nodular variant [30] over decades in Switzerland.

Our results confirm that the prognostic classification of FTC on the basis of invasiveness is valid. The outcome was unfavourable in 10/62 patients with grossly invasive FTC, in 1/45 minimally invasive FTC with VI, and in none of the 17 minimally invasive FTC with CI alone. The cause-specific disease-free survival rates at 20 years were 78% for grossly invasive and 95.5% for minimally invasive FTC ( $p = 0.0007$ ). In agreement with De Groot et al. [9], no curable recurrence was observed in FTC. No adverse outcome was noted in young (<45 yrs) patients and – independently of the patient's age – in tumours with CI alone (mean age 54 yrs). Nodal involvement (3.5%) was clinically and intraoperatively obvious, and no metachronous nodal disease occurred. Routine lymphadenectomy is therefore not indicated in FTC [1, 4, 12, 14]. Multifocal and contralateral involvement (7%) was grossly evident and led to total thyroidectomy. Our results are in agreement with studies where subgroups without deaths [9, 10] or with near 100% survival rates [11, 31] were noted, or in which hemithyroidectomy vs. total thy-

roidectomy did not adversely influence survival or recurrence [11, 12].

In definable patients without risk of systemic disease complete removal of the local tumour tissue by total primary hemithyroidectomy or total thyroidectomy is essential, whereas remnant ablation does not appear rational. Follicular neoplasia (as evidenced by high cellularity on fine needle aspiration biopsy) [32] should be treated by diagnostic primary hemithyroidectomy, avoiding ipsilateral reoperation with its increased morbidity and potentially incomplete local tumour excision [20, 22].

For PTC the multivariate age-related TNM classification [24] proved to be valuable for defining low-risk (stages I and II) and high-risk (stages III and IV) patients, with significantly different rates of survival (100% vs. 62% at 15 years;  $p < 0.0001$ ), disease-free survival (97% vs. 59%;  $p < 0.0001$ ), and recurrence-free survival (i.e. after primary treatment for cure) (96.5% vs. 80%;  $p = 0.0025$ ). Treatment strategy was radical treatment in high-risk patients and in those low-risk patients at risk for curable recurrence (N<sub>1</sub> or T<sub>4</sub> status) [4, 5, 14, 16, 21, 23, 25, 33]. Our results confirm the impact of age on survival: young (<45 yrs) patients had a mortality rate of 0% in spite of stage T<sub>4</sub> in 18%, N<sub>1</sub> in 35%, and M<sub>1</sub> in 7%. The same tumour characteristics determine a much less favourable outcome in older, i.e. high-risk patients. However, in the absence of these characteristics, i.e. in pT<sub>1-3</sub> N<sub>0</sub> M<sub>0</sub> tumours, older patients belong to the low-risk category and have an excellent prognosis, with no deaths and even with no instance of a curable recurrence in our study. Stages I and II did not have a significantly different prognosis, thus confirming the data of Hundahl et al. [8]. These authors mention the "opportunity for simplifying the current TNM prognostic system further". Our results indicate that a reduced scale of treatment may be adequate for pT<sub>1-3</sub> N<sub>0</sub> tumours, independently of the patient's age. In this subset (66% of all PTC) no death occurred, and there was only 1/36 contralateral recurrence after hemithyroidectomy and only 1/107 nodal recurrence in patients without

initial nodal involvement (though 80% had no lymphadenectomy, and 74% had no  $^{131}\text{I}$ ). After hemithyroidectomy, contralateral recurrences were noted in 4% [6], and in 14% [5, 33] of low-risk patients; several authors report very low rates (0.9%–3%) [18, 21, 33] of nodal recurrence in patients who were initially node-negative without use of radioiodine. In  $\text{pT}_{1-3} \text{N}_0$  tumours it has not been shown that  $^{131}\text{I}$  ablation offers any advantage in improving the already excellent results [16, 19]. On the other hand, radioiodine does not prevent nodal recurrence in patients with initial node disease [5, 21, 22, 34, 35]. In low-risk patients with primary lymph node metastases  $^{131}\text{I}$  is also indicated for detection and treatment of diffuse pulmonary metastases. Extensive nodal disease is a marker for disseminated pulmonary disease [21, 22, 36], which was detected in 5 (7%) of our young patients (21% of those with initial nodal disease) on the post-ablation scan (none of these patients developed a recurrence). In rare, anecdotal low-risk patients with PTC a fatal outcome was reported [37, 38]. These patients had gross invasive nodal disease [38, 39].

The question arises how radical lymphadenectomy is to be performed for detection of (occult) nodal disease, adequate staging, and stage-dependent treatment. Interestingly, no significant increase in node positivity, and no influence on therapeutic results were observed in our series with routine vs. selective lymphadenectomy [25]. In one report routine lymphadenectomy resulted in a high incidence of  $\text{N}_1$  status (82%) and to improvement of survival and recurrence [35]. More radical lymphadenectomy may itself improve therapeutic results by stage migration [40]: occult  $\text{N}_1$  tumours are eliminated from the  $\text{N}_0$  group, and  $\text{N}_1$  groups are enlarged with more favourable tumours with only occult nodal disease (Will Rogers phenomenon) [40, 41]. In sum, the impact of elective (prophylactic) node dissection on outcome remains uncertain [25].

In some apparently intrathyroidal tumours the pathologist may document penetration of the thyroid capsule. We classified these tumours as stage  $\text{pT}_4$ . Woolner et al. [3, 4] classified only tumours with gross local infiltration as "extrathyroidal" (10%; 9% in our series), without however detracting from the excellent outcome in the "intrathyroidal" and "occult" (i.e.  $\text{pT}_{1-3}$ ) categories. Ac-

cordingly, in our patients only macroscopic, but not microscopic penetration significantly influenced outcome. Special therapeutic measures such as external percutaneous irradiation are not warranted on the basis of microscopic penetration only.

Our study confirms that it is possible to select patients with FTC or PTC who require radical therapy, and those in whom technically correct hemithyroidectomy or total thyroidectomy without remnant ablation provides a virtually perfect prognosis. In PTC prognostic classification systems may accurately segregate low and high risk for death, but TNM stages I and II englobe an inhomogeneous population with respect to recurrence;  $\text{N}_1$  and/or  $\text{T}_4$  status are indicators for radical therapy in young patients with PTC. For clinical PTC without nodes we prefer total to hemithyroidectomy, to eliminate the problem of potential contralateral recurrence. However, some patients feel invalidated by loss of a vital organ and prefer hemithyroidectomy with acceptance of low risk of curable contralateral recurrence. We also favour routine (prophylactic) central lymph node dissection [1, 20, 21, 33], but the possible advantages should not be compromised by damage to the parathyroids or recurrent laryngeal nerves. In 0-risk patients cure of disease should not be compromised by postoperative iatrogenic disease (exogenous hyperthyroidism for TSH suppression) or excessive follow-up measures [1, 2, 6, 14, 23].

Are the surgeon's tactics and technique prognostic factors [37]? Capsular dissection [26, 27, 42], with fine preparatory technique is essential (a) for low morbidity in thyroid surgery [43], and (b) for oncological adequacy [20]. The technique was first used by Kocher [44, 45], who deliberately opposed it to a less subtle and anatomically different operative practice [44]; hence variance in operative technique is still of concern [27, 46]. Incomplete tumour resection may result in a fatal outcome even in low-risk patients [37, 47].

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## References

- Grebe StKG, Hay ID. Follicular cell-derived thyroid carcinomas. In Arnold A, ed. *Endocrine neoplasms*. Cancer Treat Res 1997;89:91-140.
- Cady B. Our AMES is true: How an old concept still hits the mark: or, risk group assignment points the arrow to rational therapy selection in differentiated thyroid cancer. *Am J Surg* 1997;174:462-8.
- Woolner LB, Beahrs OH, Black BM, McConahey WM, Keating FR. Classification and prognosis of thyroid carcinoma. *Am J Surg* 1961;102:354-88.
- Woolner LB. Thyroid carcinoma: Pathologic classification with data on prognosis. *Sem Nucl Med* 1971;1:481-502.
- Hay ID. Papillary thyroid carcinoma. *Endocrinol Metab Clin North Am* 1990;19:545-76.
- Cady B. Beyond risk-groups. A new look at differentiated thyroid cancer. *Surgery* 1998;124:947-57.
- Shaha AR, Shah JP, Loree TR. Low-risk differentiated thyroid cancer: The need for selective treatment. *Ann Surg Oncol* 1997;4:328-33.
- Hundahl SA, Fleming ID, Fremgen AM, Menck HR. A national cancer data base report on 53'856 cases of thyroid carcinoma treated in the U.S., 1985-1995. *Cancer* 1998;83:2638-48.
- DeGroot LJ, Kaplan EL, Shukla MS, Salti G, Straus FH. Morbidity and mortality in follicular thyroid cancer. *J Clin Endocrinol Metab* 1995;80:2946-50.
- Van Heerden JA, Hay ID, Goellner JR, Salomao D, Ebersold JR, Bergstralh EJ, et al. Follicular thyroid carcinoma with capsular invasion alone: a nonthreatening malignancy. *Surgery* 1992;112:1130-8.
- Shaha AR, Loree TR, Shah JP. Prognostic factors and risk group analysis in follicular carcinoma of the thyroid. *Surgery* 1995;118:1131-8.
- Grebe SK, Hay ID. Follicular thyroid cancer. *Endocrinol Metab Clin North Am* 1995;24:761-802.
- Hedinger CHR, in collaboration with Williams ED, Sobin LH, eds. *WHO. International Histological Classification of Tumors*. Berlin: Springer; 1988.
- Schlumberger MJ. Papillary and follicular thyroid carcinoma. *N Engl J Med* 1998;338:297-306.
- Hay ID, Bergstralh EJ, Goellner JR, Ebersold JR, Grant CS. Predicting outcome in papillary carcinoma. Development of a reliable prognostic scoring system in a cohort of 1779 patients surgically treated at one institution during 1940 through 1989. *Surgery* 1993;114:1050-8.
- DeGroot LJ, Kaplan EL, McCormick M, Straus FH. Natural history, treatment, and course of papillary thyroid carcinoma. *J Clin Endocrinol Metab* 1990;71:441-24.
- Mazzaferri EL, Jhiang SM. Long-term impact of initial surgical and medical therapy on papillary and follicular thyroid cancer. *Am J Med* 1994;97:418-28.
- Hay ID, Grant CS, van Heerden JA, Goellner JR, Ebersold JR, Bergstralh EJ. Papillary thyroid microcarcinoma: a study of 535 cases observed in a 50-year period. *Surgery* 1992;112:1139-47.
- Gemsjäger E, Heitz PhU, Martina B. Selective treatment of differentiated thyroid carcinoma. *World J Surg* 1997;21:546-52.
- Gemsjäger E, Heitz PhU, Martina B, Schweizer I. Therapiekonzept bei differenziertem Schilddrüsenkarzinom. *Praxis* 2000;89:1779-97.
- McHenry CR, Rosen IB. Prospective management of nodal metastases in differentiated thyroid cancer. *Am J Surg* 1991;162:353-6.
- Paloyan E, et al. Guidelines for the use of radio-iodine, thyroid hormone, and treatment of metastatic disease in patients with differentiated thyroid cancer. *Surg Oncol Clin N Am* 1998;7:665-80.
- Dulgeroff AJ, Hershman JM. Medical therapy of differentiated thyroid carcinoma. *Endocr Rev* 1994;15:500-15.
- Hermanek P, Sobin LH, eds. *UICC: International Union Against Cancer. TNM Classification of Malignant Tumours* (4th fully rev. ed.). Berlin: Springer; 1992.
- Gemsjäger E, Heitz PhU, Martina B, Schweizer I. Differenziertes Schilddrüsenkarzinom. Zur Chirurgie und Bedeutung von Lymphknotenbefall (in preparation).
- Reeve TS, Delbridge L, Cohen A, Crummer P. Total thyroidectomy: The preferred option for multinodular goitre. *Ann Surg* 1987;206:782-6.
- Gemsjäger E. Zur Operationstechnik bei Eingriffen an der Schilddrüse. *Chirurg* 1993;64:725-31.
- Heitz PhU, Moser HR, Staub JJ. Thyroid cancer: A study of 573 thyroid tumors and 161 autopsy cases observed over a thirty-year period. *Cancer* 1976;37:2329-37.
- Bürgi H, Supersaxo Z, Selz B. Iodine deficiency diseases in Switzerland one hundred years after Theodor Kocher's survey: A historical review with some new goitre prevalence data. *Acta Endocrinol (Copenh)* 1990;123:577-90.
- Baltisberger BL, Minder CE, Bürgi H. Decrease of incidence of toxic nodular goiter in a region of Switzerland after full correction of mild iodine deficiency. *Eur J Endocrin* 1995;132:546-9.
- Brennan MD, Bergstralh EJ, Van Heerden JA, McConahey WM. Follicular thyroid cancer treated at the Mayo Clinic 1946 through 1970: initial manifestations, pathologic findings, therapy, and outcome. *Mayo Clin Proc* 1991;66:11-22.
- Giuffrida D, Gharib H. Controversies in the management of cold, hot, and occult thyroid nodules. *Am J Med* 1995;99:642-50.
- Hay ID, Grant CS, Bergstralh EJ, Thompson GB, Van Heerden JA, Goellner JR. Unilateral total lobectomy. Is it sufficient surgical treatment for patients with AMES low-risk papillary thyroid carcinoma? *Surgery* 1998;124:958-66.
- Simon D, Goretzki PE, Witte J, Röher HD. Incidence of regional recurrence guiding radicality in differentiated thyroid carcinoma. *World J Surg* 1996;20:860-6.
- Scheumann G FW, Gimm O, Wegener G, Hundeshagen H. Prognostic significance and surgical management of locoregional lymph node metastases in papillary thyroid cancer. *World J Surg* 1994;18:559-68.
- Harness JK, Thompson NW, McLeod MK, Pasioka JL, Fukuchi A. Differentiated thyroid carcinoma in children and adolescents. *World J Surg* 1992;16:547-54.
- DeGroot LJ, Kaplan EL, Straus FH, Shukla MS. Does the method of management of papillary thyroid carcinoma make a difference in outcome? *World J Surg* 1994;18:123-30.
- Bramley MD, Harrison BJ. Papillary microcarcinoma of the thyroid gland. *Br J Surg* 1996;83:1674-83.
- Sugitani I, Yanagisawa A, Shimizu A, Kato M, Fujimoto Y. Clinicopathologic and Immunohistochemical Studies of Papillary Thyroid Microcarcinoma Presenting with Cervical Lymphadenopathy. *World J Surg* 1998;22:731-7.
- Hermanek P. Will-Rogers-Phänomen – Fakt oder Fiktion? *Chirurg* 1996;67:769-70.
- Feinstein AR, Sobin DM, Wells CK. The Will Rogers phenomenon. Stage migration and new diagnostic techniques as a source of misleading statistics for survival in cancer. *N Engl J Med* 1985;312:1804-11.
- Gemsjäger E, Schweizer I. Zuckerkandl's tuberculum in thyroid surgery. *J Am Coll Surg* 1999;188:336-7.
- Khadra M, Delbridge L, Reeve TS, Polle AG, Crummer P. Total thyroidectomy: Its role in the management of thyroid disease. *Aust N Z J Surg* 1992;62:91-5.
- Kocher T. *Chirurgie der Schilddrüse. Vergleich mit anderen Methoden. Chirurgische Operationslehre*. 5th ed. Jena: G. Fischer; 1907. p. 653.
- Halsted WS. The operative story of goitre, the author's operation. *Johns Hopkins Hosp Rep* 1920;19:71-257.
- Reeve T. Thyroid disease – role of the surgeon at the turn of the century: Introduction. *World J Surg* 2000;24:885.
- Wu HS, Young MT, Ituarte Ph, D'Avanzo A, Duh QY, Greenspan FS, et al. Death from thyroid cancer of follicular cell origin. *J Am Coll Surg* 2000;191:600-6.

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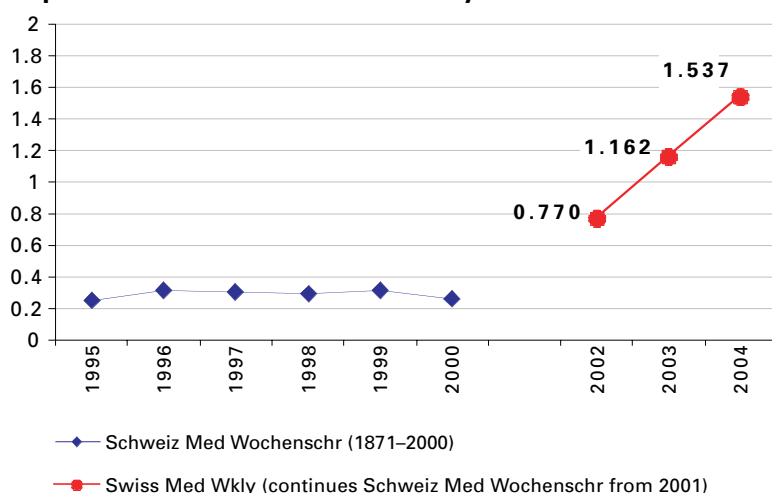
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